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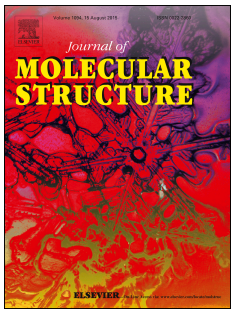

Facile synthesis and spectral characterization of 2, 5-bis (cyclohexylamino)-1, 4-benzoquinone polymorphs from methyl and ethyl protocatechuic aldehydes

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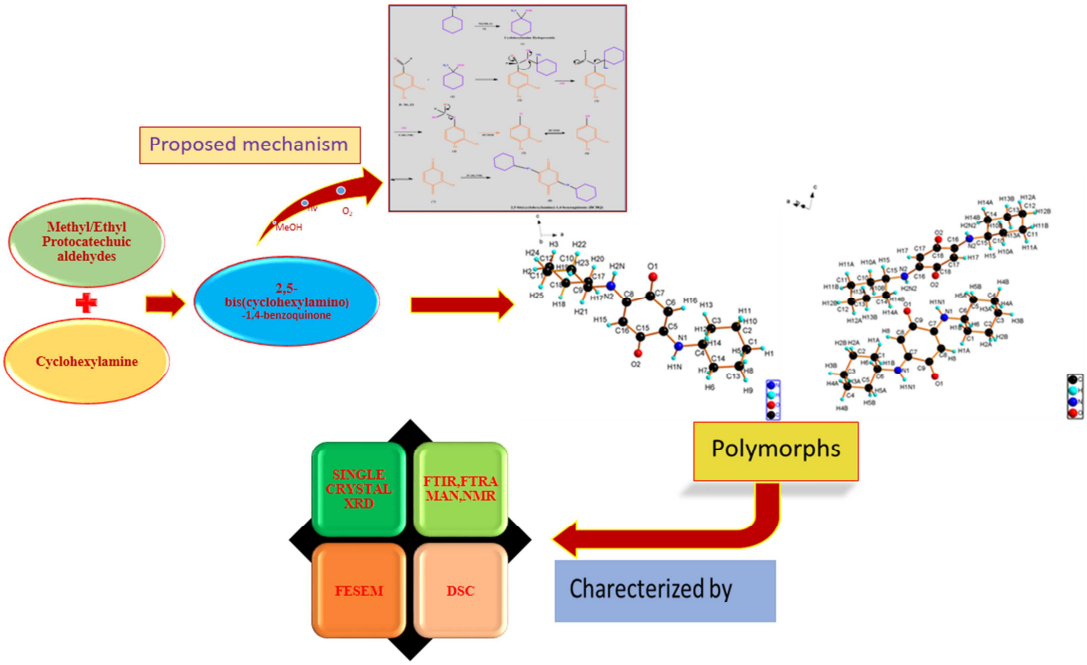

FACILE SYNTHESIS AND SPECTRAL CHARACTERIZATION OF 2, 5-BIS (CYCLOHEXYLAMINO)-1, 4-BENZOQUINONE POLYMORPHS FROM METHYL AND ETHYL PROTOCATECHUIC ALDEHYDES

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Abstract

Two polymorphs of 2,5-bis(cyclohexylamino)-1,4-benzoquinone (BCBQI&BCBQII) are synthesized by an efficient alternate method which includes the oxidation of an aromatic aldehyde to benzoquinone moiety followed by its nucleophilic substitution in a single pot. The synthesized polymorphs have been characterized and distinguished by spectral and single crystal X-ray diffraction methods. A possible mechanism for the conversion is also suggested.

Keywords: Methyl & ethyl protocatechuic aldehyde, polymorphs, aminobenzoquinone, Single crystal X-ray diffraction

Introduction

Methyl and ethyl protocatechuic aldehydes renowned under the names vanillin and ethyl vanillin are phenolic aldehydes having wide spread applications in food industry. Both the homologues are used as flavor enhancers and also as intermediate in the manufacture of certain pharmaceuticals and agrochemicals. The ethyl analogue is a broad spectrum flavor than former and is one of the most important synthetic fragrances in today's world.

In the world of synthetic chemistry, vanillin and ethyl vanillin are used extensively in the synthesis of Schiff bases and their metal complexes [1-4]. Extensive studies are carried out in the synthesis of Schiff bases by condensing a primary amine and active carbonyl compounds. From prolific literatures available for Schiff bases, those correlate cyclohexylamine and vanillin/iso vanillin/o-vanillin are being referred here. Schiff bases from vanillin and vanillal esters are synthesized by refluxing them with cyclohexylamine in methanol medium and all of them are low melting solids [5,6]. Azomethines has

also been synthesized by condensing o-vanillin with aliphatic amines like methyl amine, 2-aminopyridine and cyclohexylamine [7]. Schiff bases synthesized by condensing 2,3,4-trimethoxybenzaldehyde and cyclohexylamine can react with palladium(II) acetate in glacial acetic acid to give the acetato-bridged dimer complexes which react with sodium chloride or sodium bromide to give the corresponding halo-bridged dimers [8].

Among biologically significant natural products, ortho and para benzoquinones and their amino derivatives play a crucial role [9]. Profuse literature are available for the synthesis of naturally occurring benzoquinones [10-14]. N-substituted aminobenzoquinones are typically studied for structure/color relationships [15]. The redox potentials as well as the biological properties of 1,4-benzoquinone skeleton can be modified by the presence of suitable donor or acceptor substituents [16]. The presence of substituents carrying π-electrons and unshared electron pairs of adjacent oxygen or nitrogen atoms enhances the electron-donor properties of these quinones [17]. With the ability of undergoing reversible oxidation-reduction process, p-benzoquinones find applications in dye industry. It is also worthwhile to mention that 1,4-benzoquinone moiety forms part of ubiquinone, plastoquinone, maesaquinone, blatellaquinone etc which play vital role in biological processes including electron transport, aerobic cellular respiration, photosynthesis and plant mitochondrial respiration. Park and Crawford isolated lumiquinone A, an α-aminomalonate derived aminobenzoquinone from the entomopathogenic bacterium *Photorhabdus luminescens* TT01 from *Photorhabdus luminescens* [18].

Apart from the biosynthesis of amino benzoquinones [19], usual synthetic procedure starts from 1,4-benzoquinone or its derivatives and its subsequent nucleophilic substitution by corresponding amines. 2,5-bis (dialkylamino)-1,4-benzoquinones are synthesized by the oxidative amination of p-benzoquinone in presence of fused sodium acetate [20] and copper(II) acetate [21]. Miroslaw Dworniczak reported the concerted vinylic substitution of chlorine atoms by cyclohexylamino group at 2, 5 position in 2,3,5,6-tetrachloro-1,4-benzoquinone. The reaction has been studied spectrophotometrically in acetonitrile medium and kinetics and activation parameters are also reported [22]. 2,5-Diamino-1,4-benzoquinone was synthesized by the hydrogenolysis of 2,5-Diamino-3,6-dibromoquinone over palladium-on charcoal. Reaction procedure involves four steps with an overall yield of 82% [23]. 2, 5-dimethoxyaniline derivatives are oxidized into protected amino-1, 4-benzoquinones by using PhI $(OAc)_2$ or PhI-$(OCOCF_3)_2$ in water containing 2.5% methanol [24].

The title compound 2, 5-bis(cyclohexylamino)-1,4-benzoquinone (BCBQ) has already been synthesized by the conventional nucleophilic substitution of 1,4-benzoquinone with cyclohexylamine [25]. The synthetic procedure involves 12 hour refluxing of 1, 4-benzoquinone with cyclohexylamine in

methanol medium under aerobic conditions with 80% yield. Single crystals of BCBQ was obtained by recrystallization of the precipitate from methanol solution. It has been characterized by spectral and single crystal X-ray diffraction methods. Herein we are reporting an efficient alternate method for the synthesis of BCBQI and BCBQII from ethyl vanillin/ vanillin and cyclohexylamine in methanol medium under aerobic conditions. The polymorphs obtained show a difference only in the crystal structures. To the best of our knowledge no reports are available citing the existence of BCBQ polymorphs. Our synthetic pathway includes 1 hour refluxing of vanillin/ethyl vanillin with cyclohexylamine in methanol medium in presence of air and few drops of glacial acetic acid. Bright red crystals were separated within 7 days from the refluxed mixture which were subjected to single crystal X-ray diffraction study. A mechanism for the formation of BCBQI and BCBQII along with their complete characterization is also proposed.

Polymorphism is the ability of a molecule to exist in different crystalline forms. Polymorphs are generally characterized by the difference in some or all of the properties. They can be distinguished by various techniques of which single crystal X-ray diffraction, DSC and Raman spectrum along with FTIR need to be mentioned.

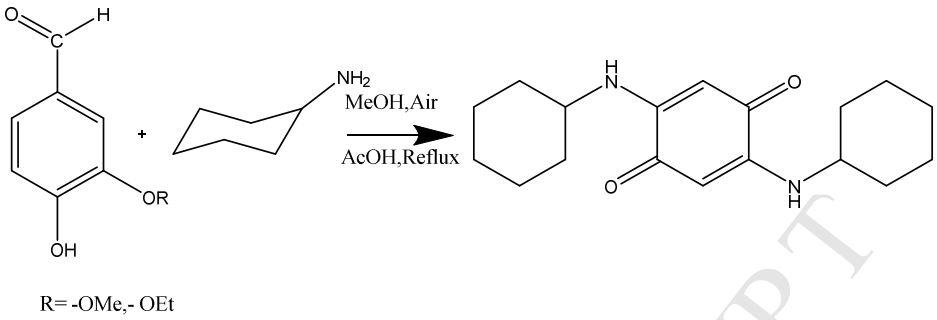
2. Experimental

2.1 Materials

Cyclohexylamine,ethyl vanillin and vanillin were of A R grade purchased from Merck and were used without any purification. Solvent used was purchased from Merck and used as received.

2.2 Synthesis of 2, 5-bis (cyclohexylamino) 1, 4-benzoquinone (BCBQ)

Cyclohexylamine (1.98 g, 20 mmol) in 20 mL methanol was refluxed with ethyl vanillin (1.66 g, 10 mmol) / vanillin (1.53 g, 10 mmol) in 20 mL MeOH in 2:1 ratio containing 6 drops of glacial acetic acid for 1 hour (Scheme1). Initial yellow color of the solution gradually changed to deep red with the progress of the reaction. Needle shaped bright red crystals of BCBQI suitable for X-ray diffraction study separated out within seven days when the aldehyde is ethyl vanillin whereas dark red block crystals were obtained for vanillin (BCBQII). It was filtered, washed with cold methanol and dried (m.p. 240°C, Yield 95%). The elemental analysis data are consistent with the formula of the compound. The compound was also characterized by IR, UV-Vis, ^{1}H, ^{13}C NMR and mass spectral techniques.



R= -OMe,- OEt

Scheme 1: Synthesis of BCBQI & BCBQII.

2.3 Physical Measurements

Analysis of carbon, hydrogen and nitrogen content of BCBQ was carried out on a Vario EL-III CHN Elemental Analyzer at the SAIF, Cochin University of Science and Technology, India. Mass spectra were recorded with JEOL GCMATE II GC-MS spectrometer with Electron Impact (EI) mode at SAIF, IIT Madras, India. IR spectra were recorded on a Perkin Elmer Infrared Spectrometer using KBr pellets in the range 4000-400 cm^{-1}. Electronic spectra were recorded in $CHCl_3$ solution on a Schimadzu UV-2450 UV-Visible Spectrophotometer. The ^{1}H, ^{13}C and 2D COSY NMR spectra were recorded using Bruker DRX-MHz NMR Spectrometer with $CDCl_3$ as solvent and TMS as the standard at the SAIF, IIT Madras, India. SEM analysis was carried out using Nova Nano SEM 450 at 15.00kV at Department. of Optoelectronics, University of Kerala. FT Raman spectra were recorded using BRUKER RFS 27 stand alone FT-Raman spectrometer in the scan range 50-4000 cm^{-1} at SAIF, IIT Madras, India. DSC curves were recorded with NETZSCH STA 449 F3 Jupiter DSC analyzer with a heating rate of 10ºC/ minute from 10ºC to 300ºC under nitrogen atmosphere at SAIF, IIT Madras, India.

2.4 X ray Crystallography

Single crystals of compounds BCBQI & BCBQII of X-ray diffraction quality were obtained from refluxed methanol solution by slow evaporation at room temperature in air. The crystallographic data and structure refinement parameters are given in Table 2. The data were collected using a Bruker AXS Kappa Apex 2 CCD diffractometer, with graphite-monochromated Mo Kα (λ= 0.71073Å) radiation. The unit cell dimensions and intensity data were recorded at 296 K. The program SAINT/XPREP (BRUKER, 2004) was used for data reduction and APEX2/SAINT (BRUKER, 2004) for cell refinement [26]. The structure solution was done using SIR92 (27] and refinement was carried out by full-matrix least squares on F^2 using SHELXL-97 [28]. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms on nitrogen atoms were refined isotropically while those on carbon atoms were

geometrically fixed and refined using riding model. Molecular graphics employed were DIAMOND Version 3.1f [29], MERCURY [30] and PLATON [31].

3 Results and discussion

BCBQI and BCBQII are synthesized in good yield (95%) by refluxing methanolic solution of vanillin (1.53 g, 10 mmol)/ ethyl vanillin (1.66 g, 10 mmol) with cyclohexylamine (1.98 g, 20 mmol) in 1:2 molar ratio in the presence of 6 drops of glacial acetic acid for 1 hr. Red needle shaped crystals of BCBQI and red block shaped crystals of BCBQII were filtered, washed with methanol and dried. BCBQI & BCBQII are found to be polymorphs. The asymmetric unit of BCBQI consist of a four molecules which belongs to monoclinic space group $P2_1/c$ while that of BCBQII consist of two molecules which is triclinic and belong to space group P1. The stoichiometries of the compounds were assigned based on elemental analysis data and are given in Table 1. Mass spectral data gives a molecular ion peak at m/z = 302 for both the polymorphs. The mass spectrum of the polymorphs are available in the supplimentary data Fig S1 & S2.

Table 1: Elemental Analysis of BCBQI & BCBQII

Compound	C, found (calc)	H, found (calc)	N, found (calc)
BCBQI	71.65 (71.50)	8.62 (8.70)	9.19 (9.30)
BCBQII	71.68 (71.50)	8.60 (8.70)	9.21 (9.30)

3.1 Crystal structure of BCBQI & BCBQII

The molecular structure of BCBQI along with atom numbering scheme is given in Figure 1. The compound crystallizes in a monoclinic space group $P2_1/c$. Unit cell of BCBQI consist of 4 molecules. Selected bond lengths and bond angles of BCBQI are given in Table 2. The C(7) − O(1) & C(15) − O(2) bond lengths (1.236 Å & 1.234 Å) are very close to the formal C═O bond length in p-benzoquinone (1.225 Å) which confirms the presence of benzoquinone moiety in BCBQI. The slight elongation of C−O bond is attributed to the hydrogen bonding network. The close proximity of C(9) −N(2) and C(4) −N(1) bond lengths (1.448 Å & 1.456 Å) shows that the quinone ring is substituted by two cyclohexylamino groups at 2 and 5 positions. All the bond angles (110.9°) and C-C bond lengths confirms the chair conformation of cyclohexyl groups in BCBQI. The C(5) − N1 & C(8) − N(2) bond lengths (1.333 Å &

1.336 Å) are intermediate of C═N bond length (1.28 Å) and C−N length (1.47 Å) which shows extended π delocalization of quinone ring.

BCBQII crystallizes in a triclinic point group P1. The molecular structure of BCBQII along with atom numbering scheme is given in Figure 1. Selected bond lengths and bond angles of BCBQII are given in Table 3. Even though the empirical formula and molecular weight of BCBQI and BCBQII are the same, the unit cell of BCBQII consist of two molecules. Detailed analysis of bond lengths and bond angles in BCBQII shows that two cyclohexyl amino rings in chair conformation are attached to the 2,5 positions in a para benzoquinone ring. Ring puckering analysis confirms the cyclohexyl C−N bond lengths of the same magnitude in BCBQI & BCBQII.

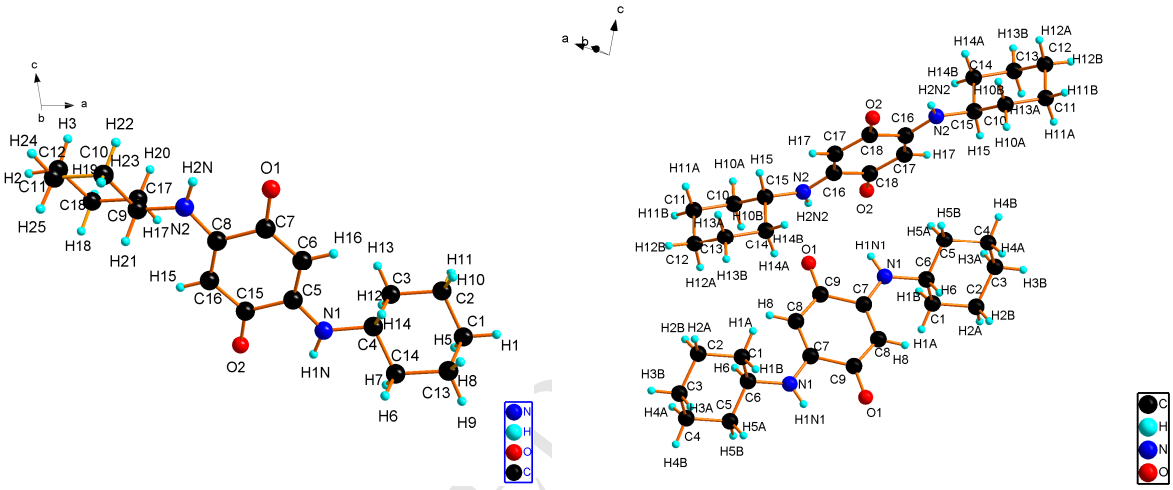


Fig 1: Molecular structures of BCBQI (left) & BCBQII (right).

Search for and analysis of solvent accessible voids in the crystal packing of BCBQII revealed a potential solvent accessible volume of approximately 17.3 $Å^3$ (844.8 $Å^3$ per unit cell volume & 2.1% of the total unit cell volume). BCBQII has 2 discrete molecules in its unit cell and the formation of even a monohydrate needs void volume of 80 $Å^3$ as a simple water molecule has a volume of about 40 $Å^3$. Thus it is clear that the crystal packing of BCBQII is solvent free as is the case of BCBQI which has no potential solvent accessible voids. This confirms that BCBQI & BCBQII are pure polymorphs.

Table 2: Selected bond lengths (Å) and bond angles (º) in BCBQI & BCBQII

BCBQI		**BCBQII**	
Bond lengths		Bond lengths	
C(1) – C(2)	1.522(3)	C(4) – C(5)	1.521(3)
C(3) – C(4)	1.512(3)	C(5) – C(6)	1.510(3)
C(4) – N(1)	1.457(3)	C(6) – N(1)	1.457(2)
C(5) – N(1)	1.332(2)	C(7) – N(1)	1.331(2)
C(5) – C(6)	1.363(3)	C(7) – C(8)	1.371(2)
C(7) – O(1)	1.236(2)	C(9) – O(1)	1.236(2)
C(15) – O(2)	1.234(2)	C(18) – O(2)	1.231(2)
C(8) – N(2)	1.337(2)	C(16) – N(2)	1.332(2)
C(17) – N(2)	1.448(2)	C(15) – N(2)	1.448(2)
Bond angles		Bond angles	
C(2) – C(1) – C(13)	111.4(2)	C(1) – C(12) − C(13)	110.67(18)
C(3) – C(4) – C(14)	110.83(19)	C(10) – C(15) –C(14)	110.66(15)
C(4) – N(1) – C(5)	124.88(18)	C(15) – N(2) – C(16)	126.16(16)
C(6) – C(5) – C(15)	120.85(16)	C(17) – C(16) – C(18b)	120.80(15)
C(16) – C(15) – O(2)	123.65(19)	C(17) – C(18) – O(2)	124.28(17)
C(8) – N(2) − C(17)	124.87(17)	C(7) –N(1) – C(6)	124.87(16)

Both inter and intramolecular hydrogen bonding exists in the crystal lattice of the polymorphs. Both the oxygen atoms O(1) and O(2) form intramolecular hydrogen bonds of same bond length (2.62Å) with N(2)H(2) & N(1)H(1) respectively in BCBQI. But in the case of BCBQII, intramolecular hydrogen bond involving N(2)H(2)−O(2) is longer (2.62Å) than that with N(1)H(1)−O(1) (2.36Å). The intermolecular H-bonds shows the reverse trend. i.e.in BCBQII, intermolecular hydrogen bonds with same bond length (3.0Å) exist between N(2)H(2)−O(1) and N(1)H(1)−O(2) while in BCBQI, slightly longer bond (3.2Å) is formed by N(2)H(2)− O(1) than N(1)H(1)− O(2) (2.9Å). Intermolecular hydrogen bonds with same magnitude in BCBQII results in a regular packing diagram than in BCBQI. Existence of hydrogen bonding is confirmed by IR spectra which shows a downward shift of C═O (stretching) from 1651cm^{-1} [32] to 1640cm^{-1} in BCBQI and to 1639cm^{-1} in BCBQII. Analysis of the donor-hydrogen and hydrogen-acceptor distances shows that inter & intramolecular H-bonds in BCBQII is little bit stronger than that in BCBQI which may be the reason for the difference in C═O stretching frequency. H- bonds of comparable strength can also be seen between C(6)−H(6)−O(1) in the polymorphs. Bond angles of H-bonds are given in Table 3. The packing diagram along with hydrogen bonding in the polymorphs are shown in Figure 2. The crystal data and structure refinement parameters of the polymorphs are given in table 4.

Table 3: H-bonds in BCBQI (top) and BCBQII (bottom)				
D-H...A	**d(D-H)(A^0)**	**d(H...A)(A^0)**	**d(D...A)(A^0)**	**<(DHA)(A^0)**
N(1)-H(1)...O(1)	0.878(19)	2.401(18)	3.201(2)	151.8(17)
N(1)-H(1)...O(2) (Intra)	0.878(19)	2.19(2)	2.624(2)	109.8(17)
N(2)-H(2)...O(1) (Intra)	0.877(17)	2.19(2)	2.621(2)	109.9(15)
N(2)-H(2)...O(2)	0.877(17)	2.185(16)	2.943(2)	144.5(16)
C(6)-H(6)...O(1)	0.98	2.5	3.436(2)	159
D-H...A	**d(D-H)(A^0)**	**d(H...A)(A^0)**	**d(D...A)(A^0)**	**<(DHA)(A^0)**
N(1)-H(1)...O(2)	0.85(3)	2.43(2)	3.095(2)	135(2)
N(1)-H(1)...O(1) (Intra)	0.85(3)	2.17(3)	2.362(2)	114(2)
N(2)-H(2)...O(2) (Intra)	0.85(2)	2.36(2)	3.082(2)	143(2)
N(2)-H(2)...O(1)	0.85(2)	2.16(2)	2.622(2)	113.8(18)
C(6)-H(6)...O(1)	0.96(2)	2.45(2)	3.393(2)	168.1(17)

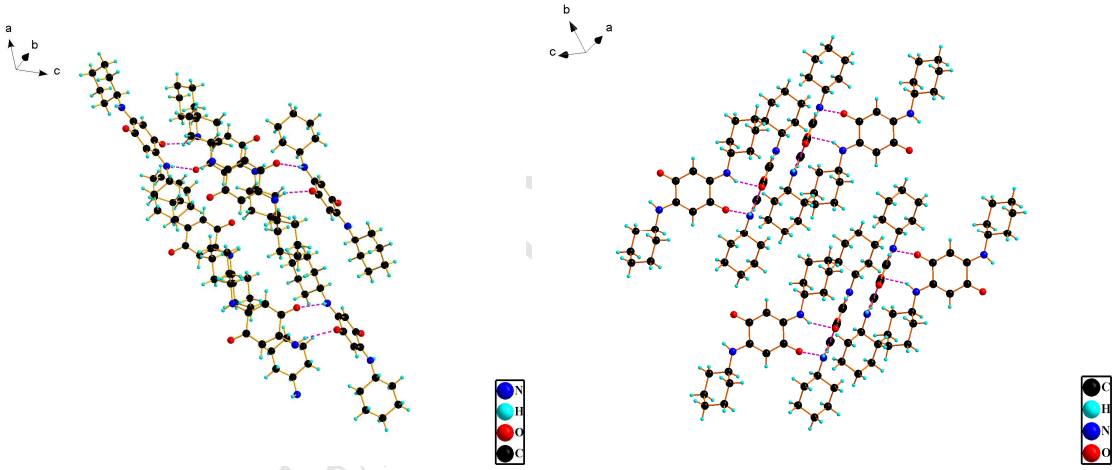


Fig 2: Packing diagram and H-bonding in BCBQI (left) & BCBQII (right)

A noticeable difference between the polymorphs lies in the existence of a CH-pi interaction in BCBQII which is absent in BCBQI. This may be due to the close proximity of 6 membered benzoquinone ring (Cg2) with C11−H11 (2.93Å) which is shown in Fig 3.

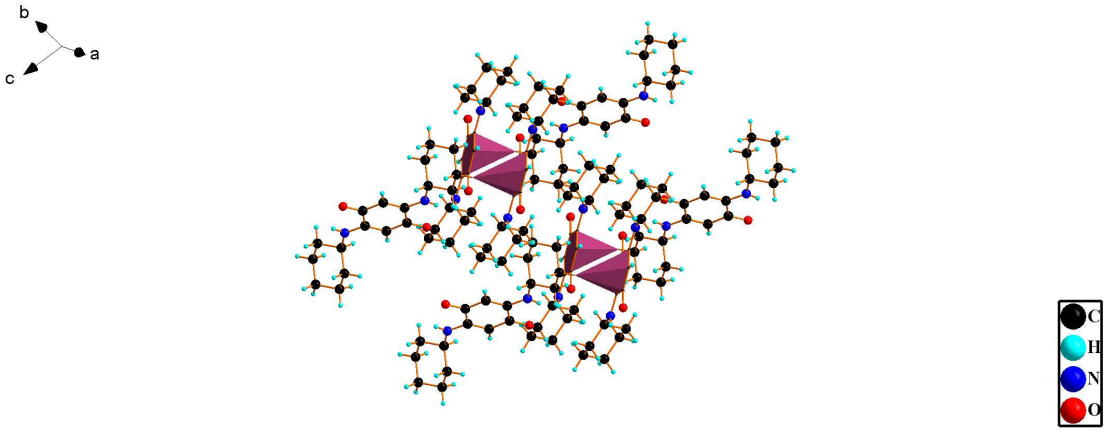


Fig 3: C-H Pi interaction in BCBQII

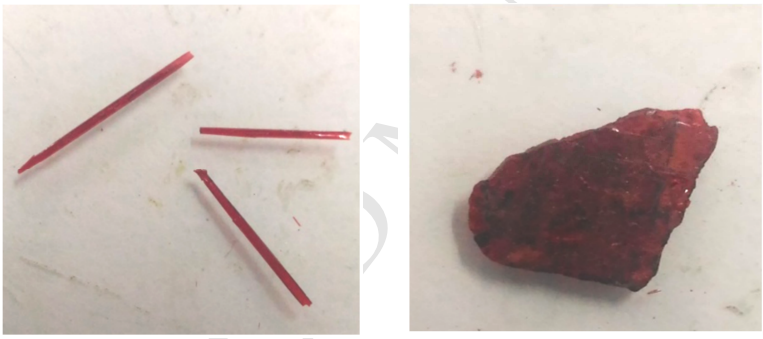


Fig 4: Crystals of BCBQI (left) & BCBQII (right)

Table 4: Crystal data and structure refinement parameters for BCBQI & BCBQII

	BCBQI	**BCBQII**
Empirical formula	$C_{18}H_{26}N_2O_2$	$C_{18}H_{26}N_2O_2$
Formula weight	302.41	302.41
Temperature (K)	296(2)	296(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Triclinic
Space Group	$P2_1/c$	P1
Unit cell dimensions		
a (Å)	14.1900(17)	6.5527(7)
b (Å)	8.9500(9)	11.3446(12)

c (Å)	13.3634(12)	12.7558(13)
Alpha (°)	90	68.681(8)
Beta (°)	99.479(5)	87.015(6)
Gamma (°)	90	73.326(6)
Volume V ($Å^3$)	1674.0(3)	844.76(16)
Z	4	2
D_{calc} (mg/m^3)	1.2	1.189
Absorption coefficient,μ (mm^{-1})	0.078	0.078
F(000)	656	328
Crystal size (mm)	0.50x0.20x0.20	0.350 x 0.300 x 0.300
Theta range for data collection (°)	1.45-28.40	3.085 - 28.313
Limiting indices	$-18 \le h \le 18$	$-5 \le h \le 8$
	$-9 \le k \le 11$	$-13 \le k \le 15$
	$-16 \le l \le 17$	$-16 \le l \le 16$
Reflections collected	13027	4069
Independent Reflections (R_{int})	4196(0.0335)	4069 (0.0199)
Completeness to theta	28.40° (99.3%)	25.242 º (98.8 %)
Absorption correction	Semi-empirical from equivalents	
Maximum and Minimum Transmission	0.9845 and 0.9619	0.9751 and 0.9554
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4164 / 0 / 200	4206 / 0 / 215
Goodness-of-fit on F^2	1.036	0.991
Final R indices [I>2sigma(I)]	R_1 = 0.0583	0.0568
	wR_2 = 0.1776	0.1529
R indices (all data)	R_1 = 0.1046	0.0873
	wR_2 = 0.2162	0.1745
Largest diff. peak and hole ($e.Å^{-3}$)	0.251 and -0.185	0.187 and -0.198

3.2 IR spectra

The FTIR spectra of BCBQI and BCBQII are shown in Fig 6. A strong band at 2852cm^{-1} corresponds to sp^3C−H (stretching) in cyclohexyl group which shows the presence of two substituted cyclohexyl rings in BCBQI. The N−H (stretching) vibration in a secondary amine is characterized by a strong band at 3271cm^{-1}which proves the presence of two secondary amino groups in BCBQI. The shifting of N−H stretching vibration towards low wave number is attributed to the presence of H-bonding in the form of N−H···O [33]. A strong band at 1640cm^{-1} is characteristic of keto group in p-benzoquinone which shows a downward shift which may be due to the hydrogen bonding. C═C (stretching) band at

1563cm^{-1} confirms the benzoquinone moiety in BCBQI. The electronic spectral data also supports the presence of a quinone ring involved in hydrogen bonding in BCBQI and BCBQII. The assignments for some selected frequencies are summarized in Table 5.

The polymorph BCBQII shows almost similar absorption frequencies. sp^3C-H (stretching) in cyclohexyl group appears at 2853 cm^{-1} and a strong peak at 3269 cm^{-1} corresponds to N−H (stretching) vibration. The C═C (stretching) peak of benzoquinone moiety in BCBQII appears at 1562 cm^{-1}. The C═O stretching vibration occurs at 1639 cm^{-1} which shows a slight downward shift which may be due to the hydrogen bonding network.

The slight difference in frequencies for the polymorphs is evident from the table. The spectra of the polymorphs appear almost identical. The differences in intermolecular and lattice vibrations due to the different ordering in the crystal lattice are responsible for variations within the spectra. Density functional studies has also been carried out for structure and vibrational spectra of transient intermediates of p-benzoquinone[34]. Nonella et al has studied the IR spectrum of p-benzoquinone in water obtained from QM/MM hybrid molecular dynamic simulation[35].

Table 5: IR assignments in BCBQI and BCBQII

Wavenumber(cm^{-1})		Assignment
BCBQI	BCBQII	
1640	1639	υC═O(Stretching)
1563	1562	υC═C(Stretching)
2852	2853	υC–H(Stretching) Cyclohexyl
3270	3269	υN–H(Stretching) 2^0 amine
1091	1088	υC–N (Stretching)

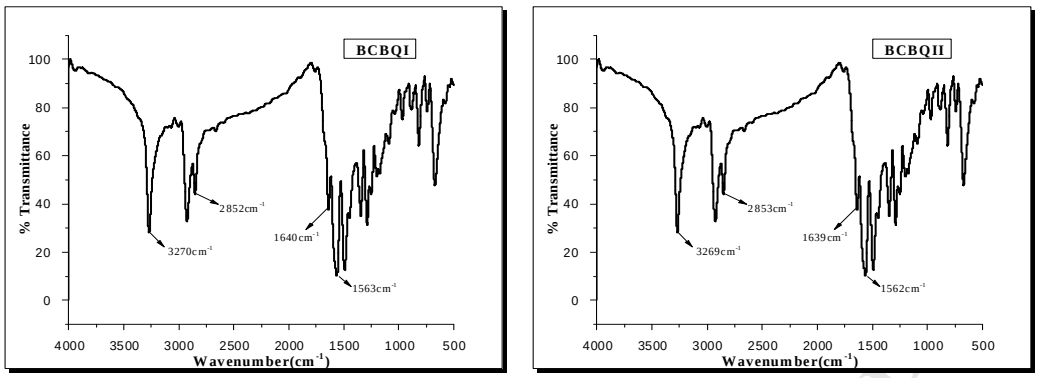


Fig 5: FTIR spectra of BCBQI (left) & BCBQII (right)

3.3 FT Raman spectra

Raman spectroscopy being a vibrational spectroscopic technique, yields important information which is related to the geometric structure of a molecule and its environment. Changes in crystal packing geometries cause band shifts or changes in relative intensity. FT Raman spectrum of the polymorphs were recorded on a Bruker RFS 27 stand alone spectrophotometer with 50-4000 cm^{-1} scan range and 2 cm^{-1} resolution. The C−H stretching vibration in BCBQI is at 3066 cm^{-1} while it is at 3064cm^{-1} in BCBQII. The C═C stretching frequencies at 1592 cm^{-1} & 1517 cm^{-1} appears to be similar in the polymorphs. The δCH_2 peak at 1142 cm^{-1} also shows similarity. The C−N inplane bending absorption appears at 440 cm^{-1} while βCH_2 antisymmetric stretching frequencies of cyclohexyl rings appear at 2931cm^{-1} in both the polymorphs. An additional absorption frequency at 971cm^{-1} in BCBQII is due to the ring puckering which is absent in BCBQI. Similarly BCBQII gives an absorption at 847 cm^{-1} due to γ CH_2 wagging and 554 cm^{-1} due to β CH_2 wagging which are absent in BCBQI. Few more additional peaks at 695 cm^{-1}, 309 cm^{-1} & 269 cm^{-1} appear in the spectrum of BCBQII which may be due to the different crystalline nature of the polymorphs. The Raman spectra of the two polymorphs are given in Fig 6.

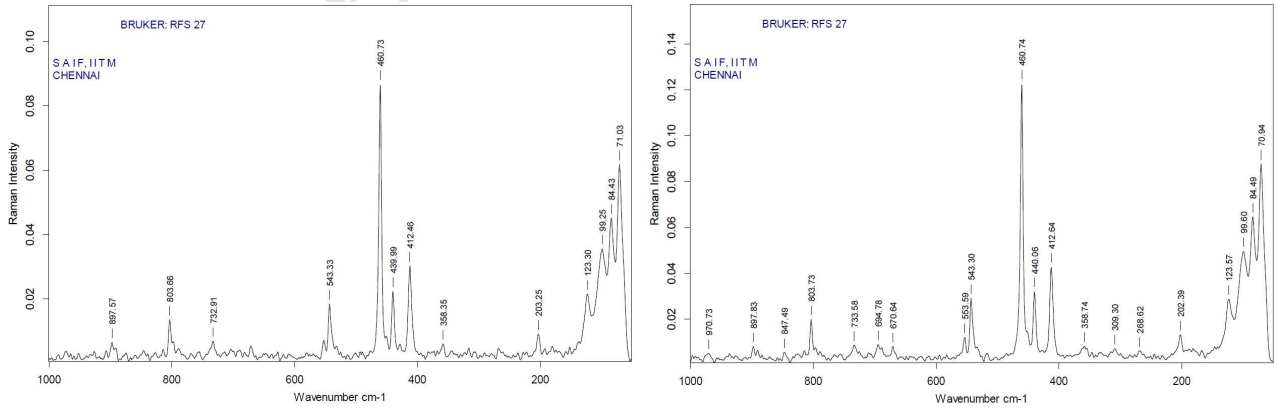


Fig 6: FT Raman spectra of BCBQI (left) & BCBQII (right)

3.4 Electronic Spectra

The UV-Visible spectra of the polymorphs were taken on a Varian, Carry 5000 spectrophotometer in $CHCl_3$.The electronic spectrum of unsubstituted parabenzoquinone is characterized by an n→π* transition at 439nm and an allowed and forbidden π→π* transitions at 240nm and 288nm [36]. The presence two cyclohexylamino substituents produces a bathochromic shift of n→π*transition to 445nm and π→π* transitions to 306nm and 395nm in BCBQI. While in the polymorph BCBQII, n→π* transition appears at 453nm and π→π* transitions at 305nm & 390nm. The weak nature of n→π* transitions compared to π →π* may be due to the existence of H-bonding network which provides a stiff structure and prevents the rotation of cyclohexylamino group around C−N bond. This will prevent the n orbit on nitrogen atom in overlapping with pi orbital on quinone ring to make n→π* transition. Theoretical interpretations of the electronic bands of 1,4-benzoquinones [37,38] and its derivatives has also been carried out by various methods[39,40].

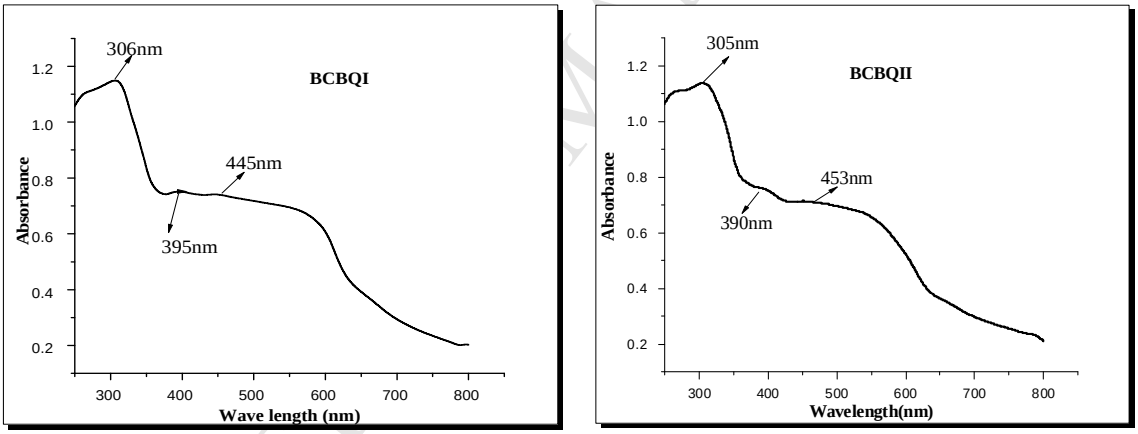


Fig 7: Electronic Spectra of BCBQI and BCBQII

3.5 ^{1}H NMR spectra

^{1}H and ^{13}C NMR spectra of the title compounds were recorded in $CDCl_3$ on Bruker Avance III, 400MHz spectrometer. ^{1}H NMR: $CDCl_3$, 400MHz, ppm. A doublet at 6.606 ppm in the spectrum of BCBQI corresponds to the vinylic protons in the benzoquinone moiety. A singlet at 5.330 ppm indicates the two protons on nitrogen atom which is shifted up field due to intramolecular hydrogen bonding between N1(H1)− O2 & N2(H2)− O1 is evident from the crystal structure. A multiplet at 3.2 ppm represents the two protons on cyclohexyl ring carbon attached to nitrogen atom. 8 hydrogen atoms (axial & equatorial) on C (17), C (10), C (3) & C (14) forms a multiplet at 1.7 ppm. Four axial protons on C (2),

C (11), C (10) & C (13) forms a multiplet at 1.6 ppm whereas the corresponding equatorial protons form a multiplet at 1.3 ppm. Axial and equatorial protons on C (1) & C (12) forms a multiplet at 1.28 & 1.21 ppm.

Even though certain resonance peaks can be observed at identical chemical shifts, the NMR spectra of the polymorphs contain nonequivalent resonance peaks. This effect arises due to the different crystal structures of the polymorphs which results in shifting of certain resonance peaks in the spectrum. The vinylic protons in benzoquinone moiety of BCQII forms a doublet at 1.606 ppm just like BCBQI. The singlet peak at 5.329 ppm corresponds to hydrogen bonded N1 (H1) and N2 (H2) which is slightly shifted from the corresponding peak in BCBQI. The H (6) & H(15) forms a sharp singlet at 3.256 ppm in place of the multiplet in BCBQI. The multiplet at 1.7 ppm in BCBQI is replaced by a doublet in BCBQII which again confirms the polymorphic behavior of BCBQI & BCBQII.

The COSY spectra were used to identify coupled spin systems in the molecule as well as spins that were adjacent within a given spin system. The off diagonal spots at 6.6 ppm & 3.2 ppm in the COSY spectra shows the correlation between vinylic proton in benzoquinone moiety [C(16) & C(6) in BCBQI and C(8) & C(17) in BCBQII] with proton on cyclohexyl ring carbon attached to nitrogen atom. Off diagonal correlation spots at 1.3 ppm & 3.2 ppm also shows the coupling between cyclohexyl proton present on carbon attached to nitrogen with those ortho to the same carbon atom. The proton present in nitrogen atom does not give any cross peaks which shows that it does not involve in coupling with adjacent protons. Similar is the case of protons at 1.6 ppm & 1.7 ppm.

3.6 ^{13}C NMR spectrum

The ^{13}C NMR spectrum provides direct information about the carbon skeleton as given in Table8. There are seven unique carbon atoms in the molecule which gives a total of 7 peaks in the spectrum. C(7) and C(15) carbon atoms of benzoquinone ring gives a singlet at 178.02 ppm which shows an up field shift due to the presence of a nitrogen atom with lone pair of electrons. C(6),C(5) & C(8),C(16) of benzoquinone moiety also show an up field shift and gives a peak at 92.69 ppm. Carbon atoms present in cyclohexyl rings can also be clearly distinguished from the peaks. The ^{13}C spectra acquired for polymorphs BCBQI and BCBQII show distinct ^{13}C resonance shifts from each other which is evident from Table 6.

Table 6: ^{13}CNMR assignments of BCBQI & BCBQII (ppm)

BCBQI	Chemical shift	BCBQII	Chemical shift
C(7) & C(15)	178	C(9) & C(18)	178
C(5) & C(8)	150	C(7) & C(16)	150
C(6) & C(16)	93	C(8) & C(17)	93
C(4) & C(9)	51	C(6) & C(15)	51
C(3), C(10),C(14), C(17)	32	C(1),C(5), C(10),C(14)	31.99 &31.67
C(1) & C(12)	25	C(3) & C(12)	25.37 & 25.23
C(2), C(11), C(13), C(18)	24	C(2),C(4),C(11),C(13)	24.61 &24.48

3.7 Field Emission Scanning Electron Microscopic analysis of polymorphs

Scanning electron microscopy being superior to optical microscopy finds application in the discrimination of polymorphs. SEM generates high-resolution images and precisely measures very small features and objects. The external morphology of the polymorphs can clearly be identified by SEM images [41]. The needle type and block type morphology of BCBQI & BCBQII can clearly be distinguished by 1000× magnified images shown in Figure 8.

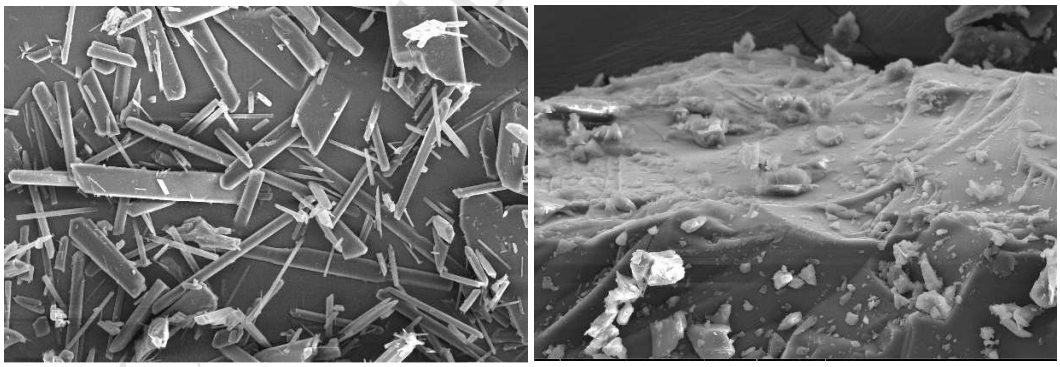


Fig 8: A 1000× magnified FESEM images of BCBQI (left) & BCBQII (right)

A 25,000× magnified image shows a layer like structure for BCBQII. The morphology as well as magnified images of the polymorphs are shown in Figure 9 which clearly distinguishes both.

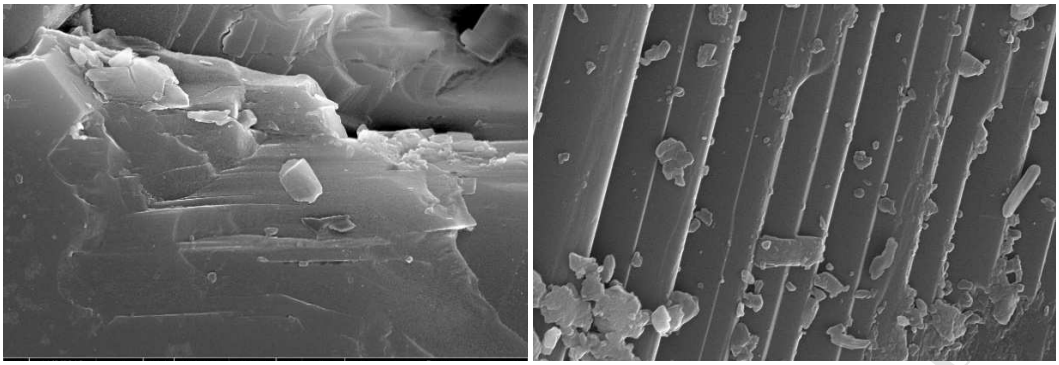


Fig 9: A 25,000× magnified images of BCBQI (left) & BCBQII

3.8 Thermal analysis of the polymorphs

On heating BCBQI and BCBQII on a watch glass on a hot plate, block shaped BCBQII started to change its appearance followed by melting. This shows that BCBQII undergo some kind of solid-solid transition before melting which is confirmed by the differential scanning calorimetric analysis of the polymorphs. Being a thermo mechanical analysis, DSC provides useful information for the identification and confirmation of polymorphs. DSC analysis was performed from 10ºC to 300ºC at a heating rate of 10ºC/ minute under nitrogen atmosphere on a NETZSCH STA 449 F3 Jupiter DSC instrument. The DSC of BCBQII shows two thermal events: a small exothermic event at 183.5ºC which represents the solid-solid phase transition and sharp endothermic event at 240ºC which is the melting point of BCBQII and BCBQI. Thus DSC provides a clear distinction between the two polymorphs with 183.5ºC as the transition temperature between the two and 240ºC as their melting point as shown in figure 10.

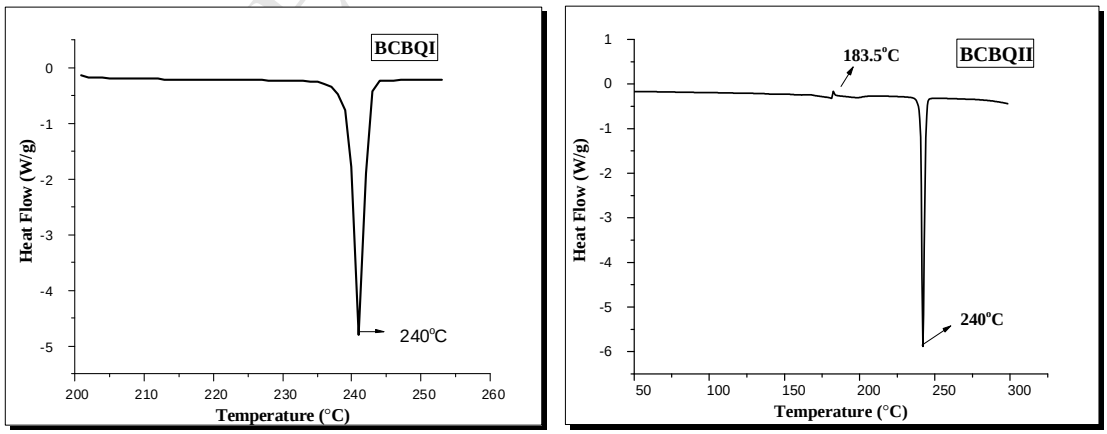


Fig 10: DSC Curves of BCBQI (left) & BCBQII (right)

3.9 Proposed mechanism

We suggest that the mechanism shown in Fig 11 may be operative. The photo oxidation of cyclohexylamine in methanol medium can give an adduct cyclohexylamine hydro peroxide [42]. Dakin oxidation can convert hydroxy benzaldehydes to benzoquinones using H_2O_2/base. Here cyclohexylamine hydro peroxide may play the role of H_2O_2/base just like urea-H_2O_2 adduct [43]. CHA adduct may add to carbonyl carbon atom and reaction proceeds like Dakin reaction. Resulting 2-ethoxy-1, 4-benzoquinone undergoes nucleophilic substitution by cyclohexylamine to give BCBQI & BCBQII. Primary amines may reversibly form imines with quinones, but the isolatable products are the less labile quinone substitution products [44].

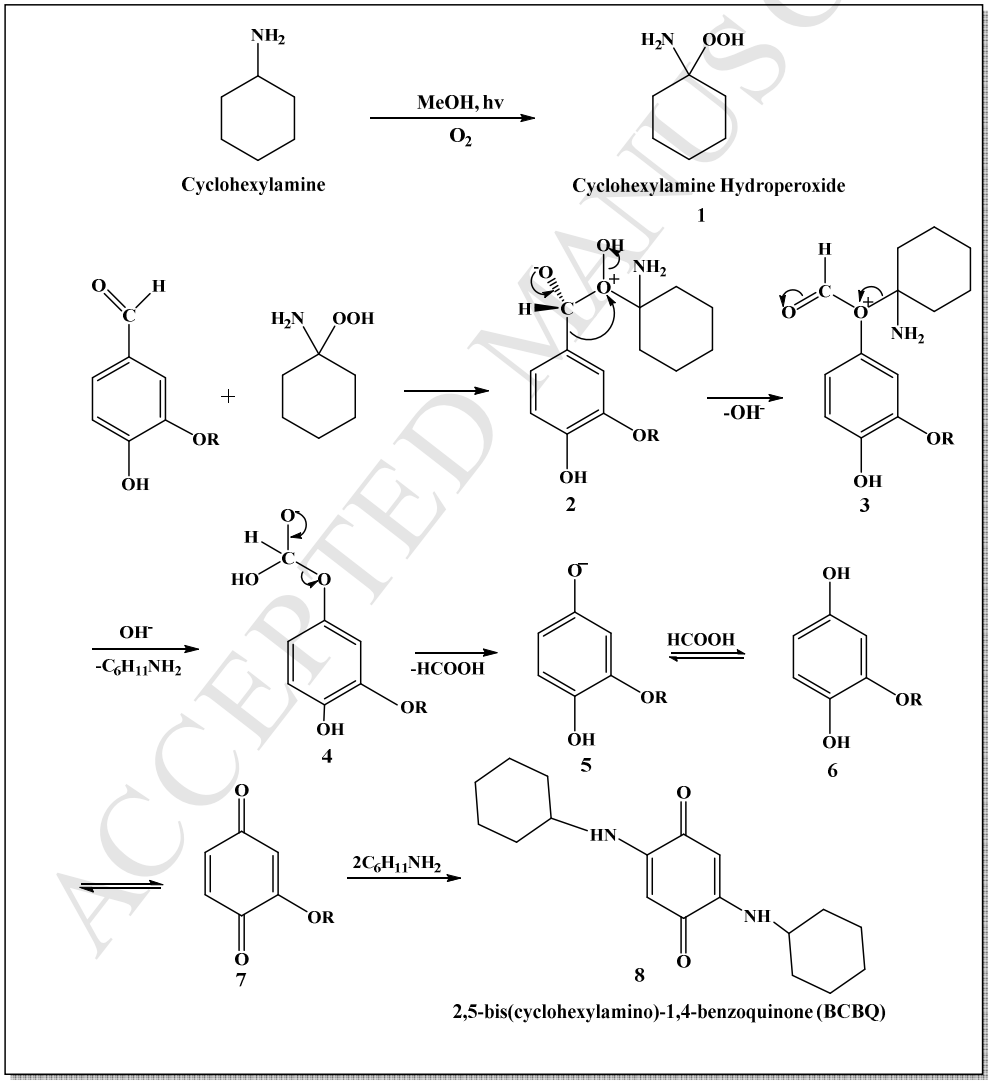


Fig 11: Proposed mechanism of formation of BCBQI& BCBQII

Conclusion

The flavoring agents, vanillin and ethyl vanillin have been converted into 2,5-bis(cyclohexylamino)-1,4-benzoquinone polymorphs which find application in dye industry. Cyclohexylamine acts both as an oxidizer for vanillins and as a nucleophile for intermediate p-benzoquinone. The whole reaction occurs in a single pot taking only 1 hr refluxing time. Bright red crystals of BCBQI & BCBQII which are polymorphs showing difference only in crystal structure were characterized and distinguished spectroscopically and by single crystal X-ray diffraction. A possible mechanism has also been suggested.

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Appendix A: Supplimentary Material

CCDC 1531838 and 1531839 contain the supplimentary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- Two polymorphs of 2,5-bis(cyclohexylamino)-1,4-benzoquinone are synthesized from methyl/ethyl protocatechuic aldehydes and cyclohexylamine.
- A mechanism involving oxidation of aromatic aldehydes by generated aminehydroperoxide to benzoquinone moiety followed by its nucleophilic substitution has been proposed.
- The synthesized polymorphs belonging to different crystal systems are characterized and distinguished by Single Crystal XRD, FTIR, FTRAMAN, NMR, FESEM and DSC analysis.